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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,186	08/17/2001	Melwyn A. Abreo	0125-0049US	1376

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,186	ABREO ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *3-6,9-38 and 43-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1,2,7,8 and 39-42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/19/01 & 7/12/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-92 are pending.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 2, 7, 8, and 39-42, drawn to a polynucleotide encoding mutant endoplasmic reticulum-associated amyloid β-peptide-binding protein (ERAB), a vector, and a host cell, classified in class 435, subclass 325.

II. Claims 3, 4, 25-38, 71, and 72, drawn to a mutant ERAB, classified in class 435, subclass 189.

III. Claims 5, 6, and 9-24, drawn to a crystal structure of mutant ERAB, classification unknown. The claims are directed to an intrinsic property of ERAB, and therefore it can't be classified.

IV. Claims 43-57, 73-76, and 88-91, drawn to a method of identifying compound that bind to ERAB, classified in class 702, subclass 19.

V. Claims 58-70, and 77-87, drawn to a method of using computer processor, classified in class 700, subclass 90+.

VI. Claim 92, drawn to a computer readable medium, classified in class 369.

The inventions are distinct, each from the other because of the following reasons:

Inventions I, and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are independent chemical entities and require different searches in the patent and non-patent literature.

Inventions I, and those of III-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case:

(a) The nucleic acid of invention I has a different function from that of the crystal structure of invention III;

(b) The methods of inventions IV and V do not utilize the nucleic acid of group I; and

(c) The nucleic acid of I and the computer readable medium of VI are not disclosed as being usable together, and have different function.

Inventions II, and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In

the instant case, the different inventions have different functions and are not disclosed as capable to use together.

Inventions II, and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the mutant ERAB can be used in a different method such as in the chemical transformation of L-hydroxyacyl-CoA.

Invention II, and those of inventions V, and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case:

(a) The method of invention V does not utilize the mutant ERAB of invention II; and

(b) Inventions II, and VI have different functions and are not disclosed as capable to use together.

Inventions III, and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the structure of mutant ERAB can be used in a different method such as in a method of identifying ERAB mutant with desired properties such enhanced thermal stability or determining the structure of closely related proteins.

Invention III, and those of inventions V, and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, inventions II, and those of inventions V and VI have different functions and have different mode of operation.

Invention IV, and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the different inventions are independent methods having different steps and products.

Inventions IV, and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially

different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the method of invention IV can be practiced without the aid of a computer, whereas the computer readable medium can be used in different methods such as in determining the structure of unknown protein as well as in modeling methods.

Inventions V, and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the method of invention V can be practiced without the aid of the computer readable medium, whereas the computer readable medium can be used in different methods such as in determining the structure of unknown protein as well as in modeling methods.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Brian Zalinski on June 26, 2003 a provisional election was made without traverse to prosecute invention I, claims 1, 2, 7, 8, and 39-42. Affirmation of this election must be made by applicant in replying to this Office action. Claims 3-6, 9-38, and 43-92 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. The specification contains sequences in Figure 2 which are not identified by a sequence identification number either in the figure or the Figure description. In addition other figures identify amino acid residues without identifying the sequence from which they are taken. The insertion of the sequence identification number in the figure description would obviate this objection. In addition, references to specific mutants are not identified by a sequence identification number, see for example page 72, line 7. Again, the insertion of SEQ ID NO: 2 after C214R would obviate this objection and the like. Similarly, the insertion of SEQ ID NO: 2 in the heading for Tables 2 would obviate this objection.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim 1 is objected to because the chemical name "L-3-hydroxyacryl-CoA" should be -----L-3-hydroxyacyl-CoA-----. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 39, and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 39, and 41 are directed to all possible nucleic acid sequences encodes a mutant endoplasmic reticulum-associated amyloid β-peptide-binding protein (ERAB) or L-3-hydroxyacyl-CoA reductase type II (HADH2) in which the protein engineered to avoid cysteine oxidation, vectors and host cell. The specification, however, only provides a single representative species from human brain encompassed by these claims in which the three-cysteine residues of the human protein are substituted individualy or in combination. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species or any other method of engineering the protein to avoid cysteine oxidation. The specification also fails to describe additional representative species of these nucleic acids by any identifying structural characteristics or properties other than the activities recited in claim 1, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. The incorporation of the embodiment of claim 2 into claim 1 would obviate this rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 2, 7, 8, and 39-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrase "ERAB or HADH2" in claims 1, 2, 7, 8, 39, and 41 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. ERAB and HADH2 are identical proteins and could not be distinguished from one another. For examination purposes only, the phrase is taken to mean "ERAB having HADH2 activity."

(b) The phrase "functional variants thereof" in claims 7, 8, and 39-40 renders the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 7, 8, and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over He *et al.* (IDSJ. Biol. Chem. 1998, 273 (17), 10741-10746) in view of the state of the art as exemplified by Zlotnick *et al.* [Acta Crystallographica, Section D, Biological Crystallography (March 1999), D55, 717-720] and Wlodawer *et al.* [Science (1989/8/11), 245, 616-621].

He *et al.* teach that human brain HADH2 is identical to ERAB which is an important factor contributing to the neuronal dysfunction of Alzheimer disease, see the abstract and the two paragraphs following the abstract. They teach the cloning of the nucleic acid sequence encoding human brain HADH2, and the amino acid encoded by said nucleic acid, see Figure 2. Figure 5 shows the alignments of the human enzyme (HB) with those bovine liver type II 3-hydroxyacylCoA dehydrogenase (BL, 89% identity) and acetoacetylCoA from *Zoogloea ramigera* (AR). Clearly, the three enzymes display substantial sequence homology wherein the cysteine residues are not conserved: C-5 of the HB is not found in the AR, C-58 corresponds to I in the AR, and C-214 corresponds to R and L in BL and AR, respectively.

Zlotnick *et al.* teach the substitution of the cysteine residues in capsid proteins of the hepatitis B virus for crystallization in order to eliminate the heterogeneity arising from oxidation, see the abstract and second column onpage 718, first and second paragraph.

Wlodawer *et al.* teach the three-dimension structure of HIV-1 protease determined by X-ray crystallography. The HIV-1 protease used in this study is made by chemical synthesis in which the two Cys residues are substituted with L-α-amino-n-buteric acid. The net effect of the substitution is substituting the thiol group of cysteine with a methyl group. The substitution is made to reduce synthetic difficulties associated with Cys deprotection and to ease product chandelling, see the Figure 1 description.

He *et al.* provide one of ordinary skill in the art to determine the structure of ERAB by X-ray crystallography as they teach the primary involvement of ERAB in Alzheimer disease. Zlotnick *et al.*, and Wlodawer *et al.* provide one of ordinary skill in the art with a motivation to substitute the cysteine residues in a protein to be crystallized to avoide problems associated with heterogeneity of the protein caused by cysteine

oxidation and the ease of handling a protein free of cysteine residues. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to substitute the one or more cysteine codone in the nucleic acid sequence encoding ERAB taught by He *et al.* with a codone encoding an isosteric amino acid residue to cystein such as isoleucine, valine or serine or another amino acid correspond to a cysteine residue in a closely related protein which are taught by He *et al.* by well known methods in the art (claims 1, 2, 7, and 8). Once the nucleic acid is made, the ordinary skill in the art would have constructed an expression vector (claims 39 and 40), transform a host cell of choice by well-known methods in the art exemplified in He *et al.* (claims 41 and 42), express the mutant ERAB, and purify it as taught by He *et al.* in order to attempt to obtain a single crystal of the mutant ERAB for structure determination. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Examiner
Art Unit 1652